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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/074,679 | 02/11/2002 | Stephen Mayo | A-71138-1/RFT/RMS/RMK | 9173 |

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EXAMINER

BORIN, MICHAEL L

ART UNIT PAPER NUMBER

1631

DATE MAILED: 05/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | | |
|------------------------------|------------------------|--|---------------------|--|
| Office Action Summary | Application No. | | Applicant(s) | |
| | 10/074,679 | | MAYO ET AL. | |
| | Examiner | | Art Unit | |
| | Michael Borin | | 1631 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 March 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14, 16 and 17 is/are pending in the application.
- 4a) Of the above claim(s) 3, 4, 8 and 9 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 5-7, 10-14, 16 and 17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1631

DETAILED ACTION

Status of Claims

1. Response to election of species requirement filed 03/15/2004 is acknowledged. Claims 1-14,16, 17 are pending. Claims 3,4,8,9 are withdrawn from consideration as drawn to non-elected species. Claims 1,2,5-7,10-14,16,17 are under consideration to the extent they are drawn to elected species of claims 2,7.

Information Disclosure Statement

2. Applicants' Information Disclosure Statements filed 03/29/2004 and 03/15/2004 have been received and entered into the application. Accordingly, as reflected by the attached completed copies of forms PTO-1449, the cited references have been considered

Claim Rejections - 35 USC § 112, second paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 13,14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

Art Unit: 1631

which applicant regards as the invention. It is not clear what constitutes a "secondary" sequence, and how are "secondary" sequences synthesized according to the claim are different from the sequences synthesized according to now amended claim 1 which already claims synthesis of modeled sequences.

Further, in regard to claim 14, it is not clear what is being shuffled in the sequence according to this method step.

Claim Rejections - 35 USC § 112, first paragraph.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1,2,5-7,10-14,16,17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method of inserting rotamers into peptide chain does not reasonably provide enablement for method of obtaining protozymes by inserting active site domains. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Art Unit: 1631

The scope of the claims is drawn to method for screening for protozymes (or enzymes) , said method comprising *in silico* inserting an active site domain of enzyme into protein scaffold, applying at least one protein design cycle, and generating a set of candidate variant proteins with putative enzyme-like activity, with subsequent synthesis and testing of the thus identified candidate variant proteins.

The only working example, Example 1 (pages 50-55) describes determination of high energy state rotamers in the chain of thioredoxin protein from *E. Coli*, and modeling and preparing thioredoxin protein with mutated residues in identified positions. The example does not demonstrate insertion of "an active site domain" as required by the claimed method. Neither there is guidance in specification on how to insert an "active" domain into a scaffold, and how to combine said insertion of the active domain with protein design so that at the end the variant protein maintains enzyme-like activity. As Brenner et al. (reference C6) discuss problems in protein design,

"... protein design is a delicate task requiring a panopy of subtle criteria to be examined and carefully balanced against each other. Most protein design experiments have failed to conclusively demonstrate that a correct fold was formed. ...In short, protein design is too complex for manual and intuitive approaches to have success on a large scale"

See paragraph bridging pages 1871 and 1872. In the instant case, there is no coherent strategy offered that would ensure that the claimed protein design method

Art Unit: 1631

would yield an protein with enzyme-like activity. Further, Desjarlais et al (reference C21) acknowledge that "designed proteins with well designed structures and properties that mimic those of natural proteins remain elusive" (see Abstract).

In view of the above, it is the Examiners position that with the insufficient guidance and working examples and in view of unpredictability and the state of art one skilled in the art could not make and/or use the invention with the claimed breadth without an undue amount of experimentation.

Claim Rejections - 35 USC § 102 and 103.

The following is a quotation of the appropriate paragraphs of 35 U.S.C.102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Art Unit: 1631

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103[©] and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1,2,5-7,13,14,16 are rejected under 35 U.S.C.102(b) as anticipated by WO 9853849.

The instant claims are drawn to a method for screening for protozymes (or enzymes) , said method comprising:

- a) identifying a suitable protein scaffold lacking a desirable enzyme-like activity;
- b) inputting a protein backbone structure of said protein scaffold into a computer, wherein said backbone structure has variable residue positions ;
- c) inserting an active site domain into said scaffold;
- d) applying at Least one protein design cycle; and
- e) generating a set of candidate variant proteins with putative enzyme-like activity;
- f) synthesizing plurality of candidate variant proteins, and
- g) testing said candidate variant proteins.

WO 9853849 describes use of computer design method, DEZYMER, to introduce a catalytically active iron superoxide dismutase site into the hydrophobic core of Escherichia coli thioredoxin, a protein normally devoid of transition metal centers. The method can be used to redesign the hydrophobic interior of a protein (e.g., thioredoxin) and thereby introduce an iron center than can catalyze the dismutation of superoxide anion.

Art Unit: 1631

6. Claims 1,2,5-7,13,14,16 are rejected under 35 U.S.C.102(b) as anticipated by admitted prior art (Hellinga et al., Robertson et al., Klemba et al). As discussed in the Background section, p. 2, lines 21-26, said references describe introducing metal binding sites into proteins.

7. Claims 10-12,16, 17 are rejected under 35 U.S.C.103(a) as obvious over WO 9853849 or Hellinga et al., or Robertson et al., or Klemba et al. in view of Brenner et al or admitted prior art.

The references are used as addressed above. If there are any differences between Applicant's claimed methods and that of the prior art, the differences would be appear minor in nature. Although the prior art do not teach all variations of the steps of the protein design, it would be conventional and within the skill of the art to select appropriate protein design steps because the techniques of computational protein design are well known in the art (see, for example, Brenner et al., or references cited on p. 2, lines 35 to p.3, line 2), and because the selection of appropriate protein design steps is conventional and within the skill in the art to which this invention pertains.

Art Unit: 1631

7. Claims 1,2,5-7,13,14,16 are rejected under 35 U.S.C. 103(a) as obvious over references teaching protein design methods (e.g., US Patents 6,188,965, US 6269,312, and other references cited on lines 35 to p.3, line 2), in view of Anderson et al. (US 6180343).

Methods of computer modeling and design of proteins, including proteins having enzyme-like activity, is well known in the art. In general, protein design methods do not specifically suggest insertion of the active domain into a backbone of enzymatically inert protein. Anderson et al. teach that insertion into a scaffold backbone (of green fluorescent protein, for example), increases conformational stability relative to linear peptides, increases steady state concentration of peptide members of peptide libraries being tested, increase cellular expression levels and decrease cellular catabolism of peptides. Consequently, it would be prima facie obvious to one skilled in the art to include insertion of a domain of a protein being modeled into an inert backbone of a scaffold, with an expectation that a protein variant designed in such fashion will feature advantageous properties described by Anderson.

Conclusion.

8. No claims are allowed

Art Unit: 1631

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (571) 272-0722.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0549.

May 26, 2004

mlb

MICHAEL BORIN, PH.D
PRIMARY EXAMINER

A handwritten signature in black ink, appearing to read 'Michael Borin', with a long, sweeping horizontal line extending to the right.